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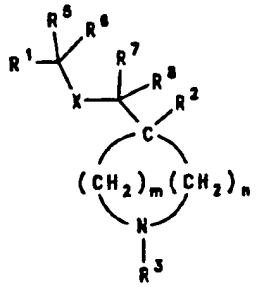
(57) Abstract

Compounds of formula (I) are tachykinin antagonists and hence useful in medicine.



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4-AMINOMETHYL/THIOMETHYL/SULFONYLMETHYL-4-PHENYLPIPERIDINES AS TACHYKININ RECEPTOR ANTAGONISTS

This invention relates to a class of azacyclic compounds, which are useful as tachykinin antagonists. More particularly, the compounds of the invention comprise an azacyclic ring system substituted by an arylmethylamino moiety.

The tachykinins are a group of naturally-occurring peptides found widely distributed throughout mammalian tissues, both within the central nervous system and in the peripheral nervous and circulatory systems. The structures of three known mammalian tachykinins are as follows:

Substance P:

Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH_2

Neurokinin A:

His-Lys-Thr-Asp-Ser-Phe-Val-Gly-Leu-Met-NH_2

Neurokinin B:

Asp-Met-His-Asp-Phe-Phe-Val-Gly-Leu-Met-NH_2

Evidence for the usefulness of tachykinin receptor antagonists in pain, headache, especially migraine, Alzheimer's disease, multiple sclerosis, attenuation of morphine withdrawal, cardiovascular changes, oedema, such as oedema caused by thermal injury, chronic inflammatory diseases such as rheumatoid arthritis, asthma/bronchial hyperreactivity and other respiratory diseases including allergic rhinitus, inflammatory diseases of the gut including ulcerative colitis and Crohn disease, ocular injury and ocular inflammatory diseases, proliferative vitreoretinopathy, irritable bowel syndrome and disorders of bladder function including cystitis and bladder detruser hyper-reflexia is reviewed in "Tachykinin Receptors and

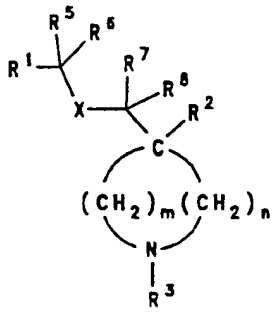
Tachykinin Receptor Antagonists", C.A. Maggi, R. Patacchini, P. Rovero and A. Giachetti, J. Auton. Pharmacol. (1993) 13, 23-93. Tachykinin antagonists are also believed to be useful in allergic conditions [Hamelet et al Can. J. Pharmacol. Physiol. (1988) 66 1361-7], immunoregulation [Lotz et al Science (1988) 241 1218-21 and Kimball et al, J. Immunol. (1988) 141 (10) 3564-9], and as anticonvulsants [Garant et al., Brain Research (1986) 382 372-8]. Tachykinin antagonists may also be useful in the treatment of small cell carcinomas, in particular small cell lung cancer (SCLC) [Langdon et al., Cancer Research (1992) 52, 4554-7].

It has furthermore been suggested that tachykinins have utility in the following disorders: depression, dysthymic disorders, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina and Reynauld's disease, fibrosing and collagen diseases such as scleroderma and eosinophillic fascioliasis, reflex sympathetic dystrophy such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, neuropathy, neuralgia, disorders related to immune enhancement or suppression such as systemic lupus erythmatosis (European patent application no. 0 436 334), conjuctivitis, vernal conjunctivitis, contact dermatitis, atropic dermatitis, urticaria, and other eczematoid dermatitis (European patent application no. 0 394 989) and emesis (European patent application no. 0 533 280).

In view of their metabolic instability, peptide derivatives are likely to be of limited utility as therapeutic agents. It is for this reason that non-peptide tachykinin antagonists are sought.

In essence, this invention provides a class of potent non-peptide tachykinin antagonists.

The present invention provides a compound of formula (I), or a salt or prodrug thereof:



(I)

wherein x is NR^4 or SO or SO_2

m is 2, 3 or 4;

n is 0, 1 or 2 when m is 2 or 3, and n is 0 or 1 when m is 4;

R^1 represents phenyl optionally substituted by 1, 2 or 3 groups selected from C_{1-6}alkyl, C_{2-6} alkenyl, C_{2-6}alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, $-OR^a$, SR^a, SOR^a, SO_2R^a, $-NR^aR^b$, $-NR^aCOR^b$, $-NR^aCO_2R^b$, $-CO_2R^a$ or $-CONR^aR^b$, where R^a and R^b each independently represent H, C_{1-6}alkyl, phenyl or trifluoromethyl;

R^2 represents phenyl optionally substituted by 1, 2 or 3 groups selected from C_{1-6}alkyl, C_{2-6} alkenyl, C_{2-6}alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, $-OR^a$, SR^a, SOR^a, SO_2R^a, $-NR^aR^b$, $-NR^aCOR^b$, $-NR^aCO_2R^b$, $-CO_2R^a$ or $-CONR^aR^b$, where R^a and R^b each independently represent H, C_{1-6}alkyl, phenyl or trifluoromethyl; heteroaryl selected from indazolyl, thienyl, furyl, pyridyl, thiazolyl, tetrazolyl and quinolyl; benzhydryl; or benzyl; wherein each heteroaryl and each phenyl moiety of benzyl and benzhydryl may be

substituted by C_{1-6}alkyl, C_{1-6}alkoxy, halo or trifluoromethyl;

R^3 represents H, COR^9, CO_2R^{10}, $COCONR^{10}R^{11}$, $COCO_2R^{10}$, SO_2R^{15}, $CONR^{10}SO_2R^{15}$, C_{1-6}alkyl optionally substituted by a group selected from (CO_2R^{10}, $CONR^{10}R^{11}$, hydroxy, cyano, COR^9, $NR^{10}R^{11}$, $C(NOH)NR^{10}R^{11}$, $CONHphenyl(C_{1-4}alkyl)$, $COCO_2R^{10}$, $COCONR^{10}R^{11}$, SO_2R^{15}, $CONR^{10}SO_2R^{15}$ and phenyl optionally substituted by one or more substituents selected from C_{1-6}alkyl, C_{1-6}alkoxy, halo and trifluoromethyl), $Y-R^{16}$ or $CO-Z-(CH_2)_q-R^{12}$;

R^4 represents H, C_{1-6}alkyl or COR^9.

R^5, R^6, R^7 and R^8 each independently represent H or C_{1-6}alkyl; or when X is NR^4, either R^5 and R^6 may together represent an oxygen atom or R^7 and R^8 may together represent an oxygen atom;

R^9 represents H, C_{1-6}alkyl or phenyl;

R^{10} and R^{11} each independently represent H or C_{1-6}alkyl;

R^{12} represents $NR^{13}R^{14}$ or an optionally substituted aromatic or non-aromatic azacyclic or azabicyclic group;

R^{13} and R^{14} each independently represent H, C_{1-6}alkyl, phenyl optionally substituted by one or more of C_{1-6}alkyl, C_{1-6}alkoxy, halo or trifluoromethyl or phenylC_{1-4}alkyl optionally substituted in the phenyl ring by one or more of C_{1-6}alkyl, C_{1-6}alkoxy, halo or trifluoromethyl;

R^{15} represents C_{1-6}alkyl, trifluoromethyl or phenyl optionally substituted by one or more substituents selected from C_{1-6}alkyl, C_{1-6}alkoxy, halo and trifluoromethyl;

R^{16} represents an optionally substituted aromatic heterocycle;

Y represents a hydrocarbon chain of 1,2,3 or 4 carbon atoms which may optionally be substituted by oxo;

Z represents CH_2, O, S or NR^{10}; and

q represents 0, 1, 2, 3, 4, 5 or 6.

As used herein, the definition of each expression, when it occurs more than once in any structure, is intended to be independent of its definition elsewhere in the same structure.

The alkyl, alkenyl and alkynyl groups referred to with respect to the formulae herein may represent straight, branched or cyclic groups, or combinations thereof. Thus, for example, suitable alkyl groups include methyl, ethyl, n- or iso-propyl, n-, sec-, iso- or tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, and cycloalkyl-alkyl groups such as cyclopropylmethyl; suitable alkenyl groups include vinyl and allyl; and suitable alkynyl groups include propargyl.

The term "halo" as used herein includes fluoro, chloro, bromo and iodo, especially chloro and fluoro.

The present invention includes within its scope prodrugs of the compounds of formula (I) above. In general, such prodrugs will be functional derivatives of the compounds of formula (I) which are readily convertible <u>in vivo</u> into the required compound of formula (I). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985. Preferably the compound of the formula (I) is the free base or a pharmaceutically acceptable acid addition salt thereof.

Those compounds according to the invention which contain one or more chiral centres may exist both as enantiomers and as diastereomers. It is to be

understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

In one apt group of compounds of the invention X is SO or SO_2.

In one favoured group of compounds of the invention X is NR^4 and R^5, R^6 R^7 and R^8 each independently represent H or C_{1-6} alkyl. In this group of compounds suitably R^5, R^6 R^7 and R^8 each represent H. In this group of compounds suitably R^5 represents methyl and R^6, R^7 and R^8 represent H.

In a further group of compounds of the invention X is NR^4 and R^5 and R^6 together represent an oxygen atom or R^7 and R^8 represent an oxygen atom.

Preferably m is 2.

When m is 2, n is preferably 2. When m is 3 or 4, n is preferably 0.

Preferably R^1 represents substituted phenyl. When R^1 is substituted phenyl suitable substituents include nitro, trifluoromethyl, trimethylsilyl, bromo, chloro, fluoro, iodo, cyano, methyl, ethyl, cyclopropyl, t-butyl, vinyl, methoxy, phenoxy, amino and carbonylmethoxy. Preferably R^1 represents phenyl substituted by one or more groups selected from C_{1-6}alkyl such as methyl or t-butyl, halo such as chloro, fluoro and bromo and trifluoromethyl. One, two or three substituents are typically present.

Preferably R^1 represents disubstituted phenyl, in particular 3,5-disubstituted phenyl, for example 3,5-disubstituted phenyl wherein the substituents are selected from C_{1-6}alkyl, halo and trifluoromethyl. More preferably R^1 represents 3,5-bis(trifluoromethyl) phenyl.

Suitable values for the group R^2 include unsubstituted or substituted phenyl, 5-membered

heteroaryl such as thienyl, 6-membered heteroaryl such as pyridyl, and benzhydryl.

Preferably R^2 represents unsubstituted or substituted phenyl.

When R^2 represents substitued phenyl a preferred substituent is halo, especially fluoro.

When R^{16} represents a substituted aromatic heterocycle, suitable substituents in the heterocyclic ring include one or more of C_{1-6}alkyl, C_{1-6}alkoxy, phenyl, oxo, thioxo, halo, trifluoromethyl, NR^aR^b, NR^aCOR^b, $CONR^aR^b$, CO_2R^a, SR^a, SO_2R^a and CH_2OR^a, where R^a and R^b are as previously defined. Particular examples of suitable substituents include methyl, methoxy, phenyl, oxo, thioxo, bromo, iodo, NH_2, SCH_3, $CONH_2$ and cyano. Particularly preferred substituents include oxo and NH_2.

Suitable values for R^{16} include thienyl, furyl, pyrrolyl, pyridyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, oxazolyl, oxadiazolyl, thiadiazolyl, isoxazolyl, quinolyl, isothiazolyl, imidazolyl, benzimidazolyl, benzoxazolyl, benzothiophenyl, benzofuranyl and indolyl, any of which may be substituted.

Preferably R^{16} represents a substituted or unsubstituted 5- or 6-membered nitrogen containing aromatic heterocycle such as for example oxazolyl, oxadiazolyl, tetrazolyl, thiazolyl, thiadiazolyl, triazolyl, pyrazinyl, pyridyl, pyrimidinyl, pyridazinyl, imidazolyl or triazinyl. More preferably R^{16} represents optionally substituted oxazolyl, oxadiazolyl, imidazolyl, thiadiazolyl, triazolyl, pyrazinyl, pyrimidinyl, pyridazinyl or triazinyl, or tetrazolyl substituted by C_{1-6}alkyl, preferably methyl. More preferably R^{16} is an unsubstituted 5-membered nitrogen containing heterocycle

or a 5-membered nitrogen containing heterocycle substituted by oxo.

It will be appreciated that, when the heterocyclic moiety R^{16} is substituted by an oxo or thioxo substituent, different tautomeric forms are possible so that the substituent may be represented as =O or -OH, or =S or -SH, respectively. For the avoidance of doubt, all such tautomeric forms are embraced by the present invention.

When R^{12} represents $NR^{13}R^{14}$, R^{13} and R^{14} are preferably both C_{1-6}alkyl such as methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl or t-butyl. More preferably R^{13} and R^{14} will both represent methyl.

When R^{12} represents an aromatic or non-aromatic azacycle or azabicycle it may contain one or more additional heteroatoms selected from O, S and N or groups NR^{16}, where R^{16} is H, C_{1-6}alkyl or phenylC_{1-4}alkyl, and may be unsubstituted or substituted. Suitable substituents include C_{1-6}alkyl, C_{1-6}alkoxy, oxo, SH, =S, halo, trifluoromethyl, NR^aR^b, NR^aCOR^b, $CONR^aR^b$, CO_2R^a and CH_2OR^a, where R^a and R^b are as previously defined.

When R^{12} represents an aromatic azacycle or azabicycle, suitable values of R^{12} include imidazolyl, triazolyl, tetrazolyl, oxazolyl, thiazolyl, pyrrolyl, pyrazolyl, pyrazinyl, pyridyl, oxadiazolyl, thiadiazolyl, isoxazolyl, isothiazolyl, benzimidazolyl, benzoxazolyl and indolyl, preferably imidazolyl, such as 2,4-imidazolyl, or pyridyl, more preferably pyridyl such as 4-, 3- or 2-pyridyl.

When R^{12} represents a non-aromatic azacycle or azabicycle, suitable values of R^{12} include morpholinyl, piperdinyl, pyrrolidinyl, piperazinyl, methylpiperazinyl, azanorbornanyl, azabicyclo[2.2.2]octanyl and azabicyclo[3.2.2]nonyl, preferably morpholinyl,

methylpiperazinyl, quinuclidinyl (azabicyclo[2.2.2] octanyl) or azabicyclo[3.2.2]nonyl, more preferably quinuclidinyl.

Suitably Y represents a hydrocarbon chain of 1 or 2 carbon atoms optionally substituted by oxo, such as CH_2, C=O, $CH(CH_3)$, $CH_2(C=O)$ or $(C=O)CH_2$. Preferably Y represents CH_2, $CH(CH_3)$ or $CH_2(C=O)$, more preferably CH_2 or $CH(CH_3)$.

Suitably q represents 0, 1, 2 or 3.

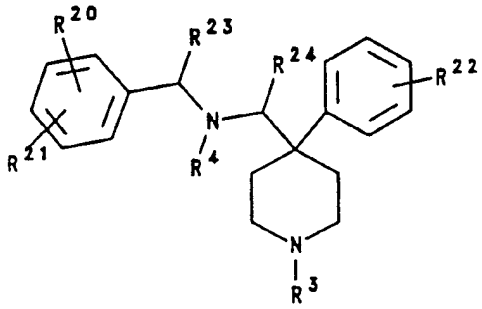
Suitable values of R^3 include H, COR^9 such as $COCH_3$, SO_2R^{15} such as SO_2CH_3, C_{1-6}alkyl such as CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$ and $CH_2CH_2C(CH_3)_3$, C_{1-6}alkyl substituted by CO_2R^{10} such as $CH_2CO_2CH_3$, CH_2CO_2H, $(CH_2)_3CO_2CH_3$ and $(CH_2)_3CO_2H$, C_{1-6}alkyl substituted by $CONR^{10}SO_2R^{15}$ such as $CH_2CONHSO_2CH_3$ and $CH_2CONHSO_2C_6H_5$, C_{1-6}alkyl substituted by phenyl, $Y\text{-}R^{16}$ and $CO\text{-}Z\text{-}(CH_2)_q\text{-}R^{12}$.

In one preferred subgroup of compounds according to the invention, R^3 represents H or C_{1-6}alkyl, more preferably H.

In a further preferred subgroup of compounds according to the invention R^3 represents $Y\text{-}R^{16}$.

Suitable values for R^4 include H, methyl and acetyl. Preferably R^4 is H or $C(=O)CH_3$, more preferably H.

A particular sub-class of compounds according to the invention is represented by compounds of formula (Ia), and salts and prodrugs thereof:



(Ia)

wherein

R^3 and R^4 are as defined for formula (I);

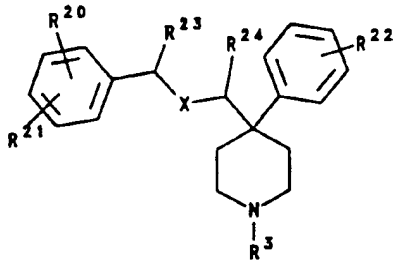
R^{20} and R^{21} independently represent H C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, OR^a, SR^a SOR^a, SO_2R^a, NR^aR^b, NR^aCOR^b, $NR^aCO_2R^b$, COR^a or $CONR^aR^b$, where R^a and R^b are as previously defined;

R^{22} represents H or halo, preferably H or fluoro; and

R^{23} and R^{24} each independently represent H or methyl.

Particular values of R^{20} and R^{21} include H, chloro, bromo, methyl, t-butyl and trifluoromethyl. Preferably R^{20} and R^{21} are both other than H and are located at the 3- and 5-positions of the phenyl ring.

A particular sub-class of compounds according to the invention is represented by compounds of formula (Ib), and salts and prodrugs thereof:



(Ib)

wherein

R^3 is as defined for formula (I), X^1 is SO or SO_2;

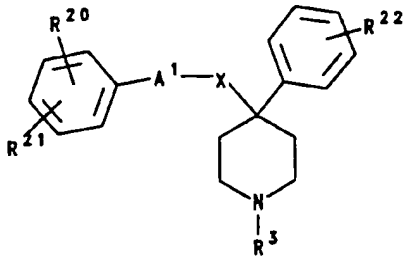
R^{20} and R^{21} independently represent H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, OR^a, SR^a SOR^a, SO_2R^a, NR^aR^b, NR^aCOR^b, $NR^aCO_2R^b$, COR^a or $CONR^aR^b$, where R^a and R^b are as previously defined;

R^{22} represents H or halo, preferably H or fluoro; and

R^{23} and R^{24} each independently represent H or methyl.

Particular values of R^{20} and R^{21} include H, chloro, bromo, methyl, t-butyl and trifluoromethyl. Preferably R^{20} and R^{21} are both other than H and are located at the 3- and 5-positions of the phenyl ring.

A particular sub-class of compounds according to the invention is represented by compounds of formula (Ic), and salts and prodrugs thereof:



(Ic)

wherein

R^3 is as defined for formula (I);

X^2 is a $C(=O)NR^4CR^6R^7$ or $CR^6R^7NR^4C(=O)$ group;

R^{20} and R^{21} independently represent H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, OR^a, SR^a SOR^a, SO_2R^a, NR^aR^b, NR^aCOR^b, $NR^aCO_2R^b$, COR^a or $CONR^aR^b$, where R^a and R^b are as previously defined; and

R^{22} represents H or halo, preferably H or fluoro.

Aptly X is a $CH_2NR^4C(=O)$, $CH(CH_3)NR^4C(=O)$, $CONR^4CH_2$ or $CONR^4CHCH_3$ group.

Particular values of R^{20} and R^{21} include H, chloro, bromo, methyl, t-butyl and trifluoromethyl. Preferably R^{20} and R^{21} are both other than H and are located at the 3- and 5-positions of the phenyl ring.

Specific compounds within the scope of the present invention include:

4-phenyl-4-(2-methoxybenzylaminomethyl)piperidine;

4-Phenyl-4-(2-Methoxybenzylaminomethyl)piperidine;

4-Phenyl-4-[(3,5-bistrifluoromethylbenzyl)amido] methylpiperidine;

1-t-Butoxycarbonyl-4-phenyl-4-[3,5-bis(trifluoromethyl)benzylthiomethyl]piperidine;

1-t-Butoxycarbonyl-4-phenyl-4-[3,5-bis(trifluoromethyl)

benzylsulphinylmethyl]piperidine;
1-t-Butoxycarbonyl-4-phenyl-4-[3,5-bis(trifluoromethyl)benzylsulphonylmethyl]piperidine;
4-Phenyl-4-[3,5-bis(trifluoromethyl)benzylsulphonylmethyl]piperidine;
4-Phenyl-4-[(3,5-bistrifluoromethyl)benzylaminomethyl] piperidine;
4-Phenyl-4-[(3,5-dichloro)benzylaminomethyl] piperidine;
4-Phenyl-4-[(3,5-dichloro)benzylamino-1-ethyl] piperidine;
4-Phenyl-4-[(3-isopropoxy)benzamidomethyl piperidine;
4-Phenyl-4-[(3-isoproxy) N-methyl-benzamidomethyl) piperidine;
and pharmaceutically acceptable salts thereof.

For use in medicine, the salts of the compounds of formula (I) will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention (such as the dibenzoyltartrate salts) or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable non-toxic acid such as hydrochloric acid, sulphuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid, phosphoric acid or p-toluenesulphonic acid. Salts of amine groups may also comprise quaternary ammonium salts in which the amino nitrogen atom carries a suitable organic group such as an alkyl, alkenyl, alkynyl or aralkyl moiety. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include

metal salts such as alkali metal salts, e.g. sodium or potassium salts; and alkaline earth metal salts, e.g. calcium or magnesium salts.

The invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, solutions or suspensions, or suppositories, for oral, parenteral or rectal administration, or topical administration including administration by inhalation or insufflation.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet

or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are adminsitered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulised by use of inert gases. Nebulised solutions may be breathed directly from the nebulising device or the

nebulising device may be attached to a face mask, tent or intermittent positive pressure breathing machine. Solution, suspension or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

For topical administration, for example as a cream, ointment or lotion, pharmaceutically acceptable carriers are, for example, water, mixtures of water and water-miscible solvents such as lower alkanols or arylalkanols, vegetable oils, polyalkylene glycols, petroleum based jelly, ethyl cellulose, ethyl oleate, carboxymethylcellulose, polyvinylpyrrolidone, isopropyl myristate and other conventionally-employed non-toxic, pharmaceutically acceptable organic and inorganic carriers. The pharmaceutical preparation may also contain non-toxic auxiliary substances such as emulsifying, preserving, wetting agents, bodying agents and the like, as for example, polyethylene glycols 200, 300, 400 and 600, carbowaxes 1,000, 1,500, 4,000, 6,000 and 10,000, antibacterial components such as quaternary ammonium compounds, phenylmercuric salts known to have cold sterilizing properties and which are non-injurious in use, thimerosal, methyl and propyl paraben, benzyl alcohol, phenyl ethanol, buffering ingredients such as sodium chloride, sodium borate, sodium acetates, gluconate buffers, and other conventional ingredients such as sorbitan monolaurate, triethanolamine, oleate, polyoxyethylene sorbitan monopalmitylate, dioctyl sodium sulfosuccinate, monothioglycerol, thiosorbitol, ethylenediamine tetraacetic acid, and the like.

The compounds of formula (I) are of value in the treatment of a wide variety of clinical conditions which are characterised by the presence of an excess of tachykinin, in particular substance P, activity. These

may include disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; epilepsy; neurodegenerative disorders such as dementia, including senile dementia of the Alzheimer type, Alzheimer's disease and Down's syndrome; demyelinating diseases such as MS and ALS and other neuropathological disorders such as peripheral neuropathy, for example, diabetic or chemotherapy-induced neuropathy, and postherpetic and other neuralgias; small cell carcinomas such as small cell lung cancer; respiratory diseases, particularly those associated with excess mucus secretion, such as chronic obstrucutive airways disease, bronchopneumonia, chronic bronchitis, cystic fibrosis and asthma, and bronchospasm; inflammatory diseases such as inflammatory bowel disease, psoriasis, fibrositis, osteoarthritis and rheumatoid arthritis; allergies such as eczema and rhinitis; hypersensitivity disorders such as poison ivy; ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, and the like; cutaneous diseases such as contact dermatitis, atropic dermatitis, urticaria, and other eczematoid dermatitis; addiction disorders such as alcoholism; stress related somatic disorders; reflex sympathetic dystrophy such as shoulder/hand syndrome; dysthymic disorders; adverse immunological reactions such as rejection of transplanted tissues and disorders related to immune enhancement or suppression such as systemic lupus erythematosis; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the neuronal control of viscera such as ulcerative colitis, Crohn's disease and incontinence; disorders of bladder function such as bladder detrusor hyper-reflexia; fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; disorders of blood flow caused by

vasodilation and vasospastic diseases such as angina, migraine and Reynaud's disease; and pain or nociception, for example, that attributable to or associated with any of the foregoing conditions, especially the transmission of pain in migraine.

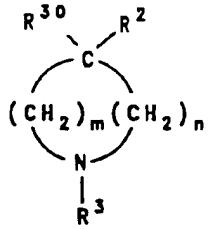
The compounds of formula (I) are particularly useful in the treatment of pain or nociception and/or inflammation and disorders associated therewith such as, for example, neuropathy, such as diabetic and chemotherapy-induced neuropathy, postherpetic and other neuralgias, asthma, osteroarthritis, rheumatoid arthritis and especially migraine.

The present invention further provides a compound of formula (I) for use in therapy. According to a further or alternative aspect, the present invention provides a compound of formula (I) for use in the manufacture of a medicament for the treatment of physiological disorders associated with an excess of tachykinins, especially substance P. The present invention also provides a method for the the treatment or prevention of physiological disorders associated with an excess of tachykinins, especially substance P, which method comprises administration to a patient in need thereof of a tachykinin reducing amount of a compound of formula (I) or a composition comprising a compound of formula (I).

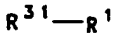
In the treatment of the conditions associated with an excess of tachykinins, a suitable dosage level is about 0.001 to 50 mg/kg per day, in particular about 0.01 to about 25 mg/kg, such as from about 0.05 to about 10 mg/kg per day. For example, in the treatment of conditions involving the neurotransmission of pain sensations, a suitable dosage level is about 0.001 to 25 mg/kg per day, preferably about 0.005 to 10 mg/kg per

day, and especially about 0.005 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

The compounds of formula (I) wherein X is NR^4 and wherein R^5 and R^6 are both H, or R^7 and R^8 are both H may be prepared by a process which comprises reacting a compound of formula (II) with a compound of formula (III):



(II)



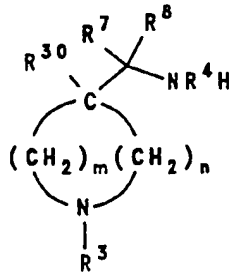
(III)

wherein R^1, R^2, m and n are as defined for formula (I), R^3 is as defined for formula (I) **except that**, when R^3 is H it is replaced by a suitable protecting group, such as $CO_2(C_{1-6}alkyl)$, R^{30} is CHO and R^{31} is $CR^5R^6NHR^4$, where R^4, R^5 and R^6 are as defined for formula (I), or R^{30} is $CR^7R^8NHR^4$, where R^4, R^7 and R^8 are as defined for formula (I), and R^{31} is CHO, followed by deprotection, if required.

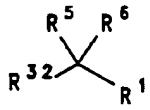
The reaction is conveniently carried out in a suitable organic solvent, such as a hydrocarbon solvent, e.g. toluene, at elevated temperature, for example, the reflux temperature of the chosen solvent.

Suitably R^{30} represents CHO and R^{31} represents $CR^5R^6NHR^4$.

Alternatively, compounds of formula (I) wherein X is NR^4 may be prepared by reaction of compounds of formula (IV) with compounds of formula (V):



(IV)



(V)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, m and n are as previously defined except that neither R^5 and R^6 and R^7 and R^8 represent an oxygen atom, and R^{32} represents a leaving group such as halo, for example chloro, bromo or iodo, or a sulphonate, for example methylsulphonate or p-toluenesulphonate, in the presence of a base.

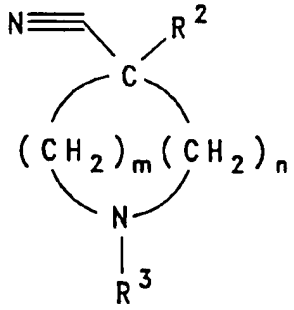
Suitable bases of use in the reaction include inorganic bases such as alkali metal carbonates, for example, potassium carbonate.

Conventiently the reaction is effected in a suitable organic solvent, for example, dimethylformamide.

Compounds of formula (I) may also be prepared from different compounds of formula (I) by interconversion processes. In particular, interconversion processes may be used to vary the groups R^3 and R^4. For example, compounds of formula (I) wherein R^3 is other than H may be prepared from the corresponding compounds of formula (I) wherein R^3 is H by conventional methods, such as reaction with a compound R^3-Hal, where Hal represents halo, in the presence of a base. Suitable reagents and conditions will be readily apparent to those skilled in the art and are illustrated by the accompanying Examples. Suitable bases include organic bases, such as tertiary amines, e.g. triethylamine, and inorganic bases, such as alkali metal carbonates, e.g.

sodium carbonate. Similarly, compounds of formula (I) wherein R^4 is C_{1-6}alkyl or COR^9 may be prepared from compounds of formula (I) wherein R^4 is H by conventional alkylation or acylation procedures. Compounds of formula (I) wherein R^3 is COR^9 may also be prepared from compounds of formula (I) wherein R^3 is H by, for example, reaction with an appropriate acid anhydride. Compounds of formula (I) wherein R^3 is C_{1-6}alkyl may be prepared from corresponding compounds of formula (I) wherein R^3 is COR^9 by reduction using, for example, borane or a borohydride such as sodium cyanoborohydride. Suitable procedures will be readily apparent to those skilled in the art. Compounds of formula (I) wherein R^3 is C_{1-6}alkyl substituted by $CONR^{10}R^{11}$ may be prepared from corresponding compounds of formula (I) wherein R^3 is C_{1-6}alkyl substituted by CO_2R^{10} by treatment with ammonia or an amine of formula $NR^{10}R^{11}$.

Intermediates of formula (II) wherein R^{30} is CHO (IIA) above may be prepared from corresponding compounds of formula (VI):



(VI)

wherein R^2, R^3, m and n are as defined for formula (II) above by reduction. Suitable reducing agents will be readily apparent to one skilled in the art and include,

for example, metallic hydrides, such as diisobutyl aluminium hydride.

The reaction is suitably carried out in an aqueous organic solvent, such as an ether, for example aqueous tetrahydrofuran.

Compounds of formula (II) wherein R^{30} is $CR^5R^6NHR^4$ (IIB) may be prepared from intermediates of formula (IIA) or (IV) by reductive amination using conventional procedures.

Where they are not commercially available, the intermediates of formula (III) above may be prepared by the procedures described in the accompanying Examples or by alternative procedures which will be readily apparent to one skilled in the art.

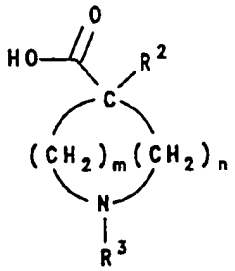
Compounds of formula (IV) may be prepared from intermediates of formula (VI) by reaction with Grignard reagents of formula R^7MgHal and/or R^8MgHal, wherein Hal represents halo such as chloro, bromo or iodo, and, for compounds of formula (IV) where R^4 is other than H, subsequent introduction of the group R^4 onto the nitrogen atom by conventional methods.

Compounds of formula (V) are commercially available or may be prepared from commercially available compounds using conventional procedures.

Compounds of formula (VI) are commercially available, or may be prepared by known procedures.

Suitable methods for the preparation of compounds of formula (VI) are described in European Patent Application no. 0 337 167, J. Am. Chem. Soc., 81, 1201 (1959), J. Med. Chem., 17, 453 (1974) and J. Med. Chem., 24, 218 (1981).

For example, compounds of formula (VI) may be prepared from the corresponding carboxylic acids of formula (VII)

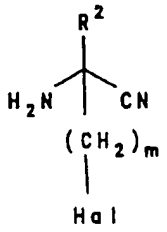


(VII)

wherein R^2, R^3, m and n are as defined for formula (I) above by reaction with hydroxylamine and treatment with formic acid.

The reaction is preferably effected at elevated temperature.

In general, compounds of formula (VI) wherein R^3 is H and n is 0 may be prepared by cyclisation of an intermediate of formula (VIII)

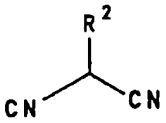


(VIII)

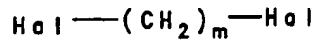
wherein R^2, Hal and m are as previously defined, in the presence of a base.

Suitable bases of use in the reaction include tertiary amines, such as, for example, triethylamine. The reaction is conveniently effected in a suitable organic solvent, such as an ether, for example, tetrahydrofuran, suitably at elevated temperature, such as the reflux temperature of the chosen solvent.

Intermediates of formula (VIII) may be prepared by reaction of compounds of formula (IX) with compounds of formula (X)



(IX)



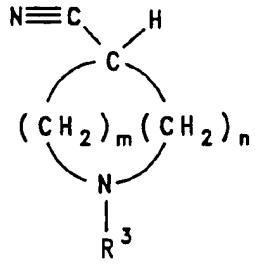
(X)

wherein R^2, m and Hal are as previously defined, in the presence of a base, followed by convertion of the isonitrile function to an amine function under standard conditions.

Suitable bases of use in the reaction include alkali metal hydrides, such as, for example, sodium hydride. The reaction is conveniently effected in a suitable organic solvent, such as an ether, for example, tetrahydrofuran, suitably at elevated temperature, such as the reflux temperature of the chosen solvent.

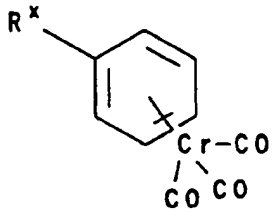
Compounds of formulae (IX) and (X) are commercially available, or may be prepared from commercially available starting materials using conventional procedures well known to those skilled in the art.

Compounds of formula (VI) wherein n is other than 0 may in general be prepared from the corresponding compounds of formula (XI)



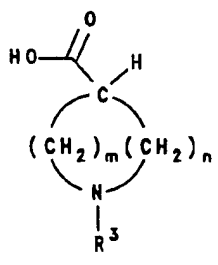
(XI)

wherein R^3 and m are as previously defined and n is 1 or 2 by treatment with a base and reaction of the resulting nucleophile with a reagent suitable to introduce the group R^2, such as an activated aryl moiety, for example



wherein R^X is H or halo, such as chloro; an aryliodide in the presence of nickel bromide (J. Am. Chem. Soc., 99, 4833 (1977)); or a hypervalent aryliodide (Synthesis, 709 (1984)).

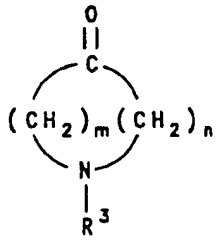
Compounds of formula (XI) may be prepared from the corresponding intermediates of formula (XII)



(XII)

wherein R^3, m and n are as defined for formula (XI) above, as described for the preparation of compounds of formula (VI) from compounds of formula (VII).

Intermediates of formula (XII) may be prepared from compounds of formula (XIII)

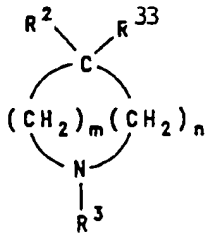


(XIII)

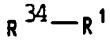
wherein R^3, m and n are as defined for formula (IX) by conventional methods, for example, by reaction with 1,3-dithiane and hydrolysis.

Still further procedures suitable for the preparation of compounds of formula (VI) will be readily apparent to those skilled in the art.

Compounds of the formula (I) wherein X is NR^4 and either R^5 and R^6 represent an oxygen atom or R^7 and R^8 represent an oxygen atom may be prepared by a process which comprises reacting a compound of formula (IIa) with a compound of formula (IIIa):



(IIa)



(IIIb)

wherein R^1, R^2, m and n are as defined for formula (I), R^3 is as defined for formula (I) **except that**, when R^3 is H it is replaced by a suitable protecting group, such as $CO_2(C_{1-6}alkyl)$, and R^{33} and R^{34} are chosen as follows:

R^{33} represents (C=O)OH and R^{34} represents $HNR^4CR^6R^7$; or

R^{33} represents $CR^6R^7NR^4H$ and R^{34} represents C(=O)Hal; or

R^{33} represents NR^4H and R^{34} represents -N=C=O; or

R^{33} represents -N=C=O and R^{34} represents NR^4H; or

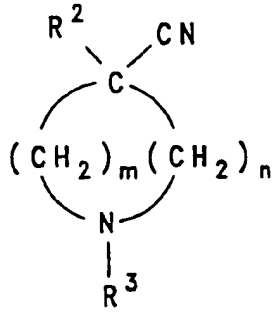
R^{33} represents O(C=O)Hal and R^{34} represents NH_2; or

R^{33} represents NH_2 and R^{34} represents O(C=O)Hal;

wherein R^4, R^6 and R^7 are as defined for formula (I) and Hal represents halo such as iodo, bromo or, preferably, chloro; followed by deprotection if, if required.

In each case the reaction is effected under conventional conditions. For example, for the formation of an amide linkage the reaction is effected in the presence of a base. Favoured bases of use in the reaction include tertiary amines such as triethylamine and alkali metal carbonates such as potassium carbonate.

Intermediates of formula (IIa) above wherein R^{33} is $CR^6R^7NR^4H$ and R^4, R^6 and R^7 all represent H may be prepared from corresponding compounds of formula (IVa):



(IV)

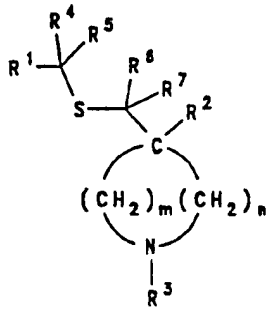
wherein R^2, R^3, m and n are as defined for formula (II) above by reduction. Suitably reduction will be effected by catalytic hydrogenation, for example, using a nobel metal catalyst such as platinum, palladium or rhodium, or oxides thereof. A preferred catalyst is platinum dioxide which is preferably used under acidic conditions, for example, using acetic acid as solvent.

Compounds of formula (IIa) wherein R^{33} is $CR^6R^7NR^4H$ and R^6, R^1 and R^4 are not all H may be prepared from intermediates of formula (IVa) by reductive amination using conventional procedures.

Compounds of formula (IIa) wherein R^{33} is COOH or COHal are commercially available, or may be prepared by known procedures. For example, suitable methods are described in European Patent Application no. 0 337 167, J. Am. Chem. Soc., 81, 1201 (1959), J. Med. Chem., 17, 453 (1974) and J. Med. Chem., 24, 218 (1981).

Compounds of formula (IIa) wherein R^{33} is -N=C=O may be prepared from corresponding compounds of formula (IIa) wherein R^{33} is NH_2 by reaction with triphosgene in the presence of a base, such as a tertiary amine, for example triethylamine.

Compounds of the formula (I) wherein X is SO or SO_2 may be prepared by oxidation of a compound of the formula (IIb):



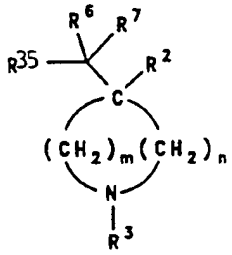
(IIb)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, m and n are as defined for formula (I).

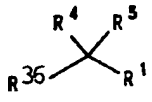
Suitable oxidising agents will be readily apparent to those skilled in the art and include peroxides, such as hydrogen peroxide and potassium permanganate, and peracids, such as m-chloroperbenzoic acid. For the preparation of a compound of formula (I) wherein X is SO, the appropriate intermediate of formula (II) is treated with one mole of oxidising agent. For the preparation of a compound of formula (I) wherein X is SO_2, the appropriate intermediate of formula (IIb) is treated with two moles of oxidising agent.

Alternatively, compounds of formula (I) wherein X is SO_2 may be prepared by oxidation of compounds of formula (I) wherein X is SO as above described.

Intermediates of formula (IIb) may be prepared by a process which comprises reacting a compound of formula (IIIb) with a compound of formula (IVb):



(IIIb)



(IVb)

wherein R^1, R^2, R^4, R^5, R^6, R^7, m and n are as defined for formula (I), R^3 is as defined for formula (I) **except that**, when R^3 is H it is replaced by a suitable protecting group, such as $CO_2(C_{1-6}alkyl)$; and one of R^{35} and R^{36} represents a leaving group and the other of R^{35} and R^{36} represents SH, in the presence of a base, followed by deprotection, if required.

Suitably R^{35} represents a leaving group and R^{36} represents SH.

Suitable leaving groups include halo, e.g. chloro, bromo or iodo, or sulphonate derivatives such as tosylate or mesylate.

The reaction is conveniently carried out in a suitable organic solvent, such as an ether, e.g. 1,2-dimethoxyethane, at a temperature in the region of 0°C. Favoured bases of use in the reaction include alkali metal amides and hydrides, such as potassium bis(trimethylsilyl)amide, sodium hydride or potassium hydride.

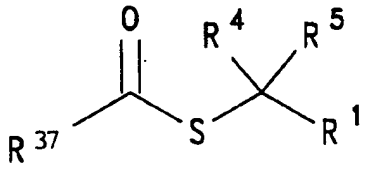
The intermediates of formula (IIIb) above wherein R^{35} is SH may be prepared from the corresponding intermediates of formula (IIIb) wherein R^{35} represents OH (hereinafter intermediates (IIIA)) by treating the latter compound with Lawesson's reagent or phosphorus pentasulphide in a suitable solvent, e.g. pyridine, at

ambient or elevated temperatures, suitably at reflux temperature.

Intermediates of formula (IIIb) wherein R^{35} is a leaving group may be prepared from intermediates of formula (IIIA) by conventional methods, such as treatment with an appropriate sulphonyl halide such as, for example, methanesulphonyl chloride or toluenesulphonyl chloride, or a thionyl halide.

Similarly, intermediates of formula (IVb) wherein R^{36} is a leaving group may be prepared from the corresponding compounds of formula (IVb) wherein R^{35} is OH by conventional methods.

Intermediates of formula (IVb) wherein R^{36} is SH may be prepared from compounds of formula (Vb)



(Vb)

wherein R^1, R^4 and R^5 are as previously defined and R^{37} represents an alkyl, alkoxy, aryl or aryloxy group, by hydrolysis.

Suitably the reaction is effected under base catalysis using, for example, an alkali metal alkoxide, such as sodium methoxide, in a suitable organic solvent such as an alcohol, for example, methanol.

Compounds of formula (Vb) may be prepared by reaction of compounds of formula $R^1CR^4R^5$-Hal, wherein R^1, R^4 and R^5 are as previously defined and Hal represents halo such as chloro, bromo or iodo, with compounds of formula R^{37}COSH, wherein R^{37} is as previously defined, in the presence of a base.

Suitable bases of use in the reaction include alkali metal carbonates such as, for example, caesium carbonate.

Where the above-described process for the preparation of the compounds according to the invention gives rise to mixtures of stereoisomers these isomers may, if desired, be separated, suitably by conventional techniques such as preparative chromatography.

The novel compounds which contain one or more chiral centres may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. For example, intermediate alcohols of formula (IIIA), wherein R^{35} is OH, may be resolved into their component enantiomers by standard techniques, such as the formation of diastereomeric esters or amides, followed by chromatographic separation or separation by fractional crystallization and removal of the chiral auxiliary. The diastereomeric alcohols can then be used to prepare optically pure compounds of formula (I).

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene and P.G.M. Wutts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The exemplified compounds of this invention were tested by the methods set out at pages 36 to 39 of international application number PCT/GB92/01241. The

compounds were found to be active with IC_{50} at NK1R of less than 150nM.

The compounds of this invention may be formulated as specifically illustrated at pages 35 to 36 of international application number PCT/GB92/01241.

The following examples illustrate this invention:

EXAMPLE 1

4-Phenyl-4-(2-Methoxybenzylaminomethyl)Piperidine Dihydrochloride

a) N-^{t}Butoxycarbonyl-4-phenyl-4-cyano piperidine

Di-^{t}butyldicarbonate (20g) was added to a stirred solution of 4-phenyl-4-cyano piperidine hydrochloride (20g) and Et_3N (9.5g) in dry dichloromethane (100ml). The resulting solution was stirred for 18 hours at room temperature. The reaction mixture was washed with water (100ml) and the organic layer separated and dried over $MgSO_4$. Filtration and removal of solvent under reduced pressure afforded a white solid. Recrystallisation from hexane gave the title compound as white needles, mp = 64°C. ^{1}H NMR (360MHz, $CDCl_3$) δ 1.46 (9H, s, $C(\underline{CH}_3)_3$), 1.90 (2H, m, C-C<u>H</u>H and C<u>H</u>H-C), 2.04 (2H, m, C-CH<u>H</u> and CH<u>H</u>-C), 3.20 (2H, m, N-C<u>H</u>H and C<u>H</u>H-N), 4.26 (2H, m, N-CH<u>H</u> and CH<u>H</u>-N), 7.26-7.49 (5H, m, Ar <u>H</u>); MS (CI^+) 287 ($M + H^+$).

b) N-^{t}Butoxycarbonyl-4-phenyl piperidine-4-carboxaldehyde

A solution of N-^{t}Butoxycarbonyl-4-phenyl-4-cyano piperidine (5.0g) in dry toluene (100ml) at -78°C was treated with a solution of DIBALH (27.7ml x 1.0mol) in toluene. The reaction was maintained at -78°C for two hours, at which time it was quenched by slow addition of a saturated solution of NH_4Cl (20ml), and allowed to warm to room temperature. The reaction mixture was poured into water (100ml) and extracted into ethyl

acetate. The organic layers were separated, dried over $MgSO_4$, filtered and solvent removed to give a yellow oil. Flash chromatography in silica gel (20% EtOAc in hexane) afforded the product as a clear oil (2.1g). ^1H NMR (360MHz, $CDCl_3$) δ 1.45 (9H, s, $C(\underline{CH}_3)_3$), 1.95 (2H, m, C-C<u>H</u>H and C<u>H</u>H-C), 2.07 (2H, m, C-CH<u>H</u> and CH<u>H</u>-C), 3.12 (2H, m, N-C<u>H</u>H and C<u>H</u>H-N), 3.85 (2H, m, N-CH<u>H</u> and CH<u>H</u>-N), 7.26-7.40 (5H, m, Ar H), 9.40 (1H, s, C<u>H</u>O); MS (CI^+) 290 ($M + H^+$).

c) <u>N-^{t}Butoxycarbonyl-4-phenyl-4-(2-methoxybenzyl aminomethyl)piperidine</u>

A solution of N-^{t}butoxycarbonyl-4-phenylpiperidine-carboxaldehyde (500mg) and 2-methoxybenzylamine (246mg) in toluene (50ml) was warmed to reflux under Dean and Stark conditions for 24 hours. After cooling to room temperature the solvent was removed under reduced pressure, and the residue re-dissolved in dry MeOH (20ml). The pH was adjusted to 4 by the addition of solid citric acid, and $NaCNBH_3$ (258mg) added. The reaction was allowed to stir at room temperature for four hours, at which time the solvent was removed under reduced pressure. The solid residue was dissolved in water, basified to pH10 and extracted into ethyl acetate. The organic layers were separated, dried over $MgSO_4$, filtered and solvent removed to afford a clear oil. Flash chromatography on silica gel (5% MeOH/CH_2Cl_2) afforded the title compound as a clear oil (400mg). ^1H NMR (360MHz, $CDCl_3$) δ 1.42 (9H, $C(\underline{CH}_3)_3$), 1.79 (2H, m, C-C<u>H</u>H and C<u>H</u>H-C), 2.04 (2H, m, C-CH<u>H</u> and CH<u>H</u>-C), 2.65 (2H, s, CH_2NH-<u>CH_2</u>Ar), 3.14 (2H, m, N-C<u>H</u>H and C<u>H</u>H-N), 3.60 (2H, s, <u>CH_2</u>-NH-CH_2Ar), 3.76 (2H, m, N-CH<u>H</u> and CH<u>H</u>-N), 3.77 (3H, s, OCH_3), 6.71 (1H, d, J = 6.0Hz, H-6'), 6.85 (1H, t, J = 6.0 and 1.0Hz, H-5'), 7.06 (1H, d, J = 6.0Hz, H-3'), 7.17 (1H, t, J =

6.0 and 1.0Hz, H-4'), 7.20-7.46 (5H, m, Ar H); MS (CI^+) 411 ($M+H^+$).

d) 4-Phenyl-4-(2-methoxybenzylaminomethyl)piperidine dihydrochloride

Dry HCl gas was passed through a solution of N-^{t}butoxycarbonyl-4-phenyl-4-(2-methoxybenzylaminomethyl)piperidine (400mg) in dry ether (50ml) at 00C for 30 minutes. The passage of gas was stopped and the solution allowed to warm to room temperature and stirred for 2 hours. The white precipitate was filtered off and re-crystallised from ethyl acetate to afford the title compound as white needles. Mp = 78-80°C. ^{1}H NMR (360MHz, DMSO) δ 2.14 (2H, m, C-CHH and CHH-C), 2.37 (2H, m, C-CHH and CHH-C), 2.69 (2H, s, N-CHH and CHH-N), 2.78 (2H, m, N-CHH and CHH-N), 3.19 (2H, s, CH_2-NH-CH_2Ar), 3.33 (2H, s, CH_2-NH-CH_2Ar), 3.57 (3H, s, OCH_3), 6.91 (1H, d, J = 6.0Hz, H-6'), 6.96 (1H, t, J = 6.0 and 1.0Hz, H-5'), 7.25 (1H, d, J = 6.0Hz, H-3'), 7.37 (1H, t, J = 6.0 and 1.0Hz, H-4'), 7.41-7.73 (5H, m, Ar H); MS (CI^+) 311 ($M+H^+$); $C_{20}H_{27}N_2O.2HCl.H_2O$ requires C, 59.70; H, 7.77; N, 6.96. Found: C, 59.36; H, 7.95; N, 6.80%.

EXAMPLE 2

4-Phenyl-4-[(3,5-Bistrifluoromethylbenzyl)amidol methylpiperidine Hydrochloride

a) 4-Phenyl-4-Aminomethyl-1-t-Butoxycarbonyl Piperidine

A solution of the compound of Example 1, part A in 15% acetic acid ethanol was hydrogenated at 50psi over platinum

dioxide (0.5g) for 18 hours. The catalyst was filtered off and the solvent removed under reduced pressure. The residue was partitioned between ethyl acetate and 2N sodium hydroxide solution. The organic extract was separated, dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to afford the pure product as a clear oil. ^1H NMR (360MHz, $CDCl_3$) δ 1.45 (9H, s, $(\underline{CH}_3)_3C$), 1.67 (2H, m, $CH\underline{H}$-CH_2N x 2), 2.20 (2H, m, $C\underline{H}H$-CH_2N x 2), 2.75 (2H, brs, $\underline{CH}_2NH_2$), 3.05 (2H, m, $CH_2CH\underline{H}N$ x 2), 3.71 (2H, m, $CH_2C\underline{H}HN$ x 2), 7.21-7.39 (5H, m, ArH); MS CI$^+$ 291 $(M+1)^+$.

b) 4-Phenyl-4-[(3,5-Bistrifluoromethylbenzyl)amido] methylpiperidine Hydrochloride

3,5-Bistrifluoromethylbenzoylchloride (110mg) was added to a stirred solution of 4-phenyl-4-aminomethyl-1-t-butoxycarbonyl piperidine (118mg) and triethylamine (55µl) in dry dichloromethane at room temperature. After two hours the reaction mixture was washed with water, the organic layer separated and dried ($MgSO_4$). Filtration and removal of solvent afforded yellow crystals. Recrystallisation from hexane, followed by deprotection using ethereal hydrogen chloride afforded the product as a white solid (172mg), mp 215-216°C. ^1H NMR (360MHz, DMSO-d_6) δ 2.07 (2H, m, $CH\underline{H}$-CH_2N x 2), 2.31 (2H, m, $C\underline{H}H$-CH_2N x 2), 2.68 (2H, m, CH_2-$CH\underline{H}N$ x 2), 3.22 (2H, m, CH_2-$C\underline{H}HN$ x 2), 3.42 (2H, s, $\underline{CH}_2N$-CO), 7.27-7.46 (5H, ArH), 8.31 (1H, s, CF_3C-$C\underline{H}$-CCF_3), 8.38 (2H, s, C-$\underline{CH}$-CCF_3 x 2); MS CI$^+$ 431 $(M+1)^+$; $C_{21}H_{20}N_2O$. HCl. $\frac{1}{2}H_2O$ requires C, 53.00; H, 4.62; N, 5.89; Found C, 53.09; H, 4.24; N, 5.81%.

EXAMPLE 3

1-t-Butoxycarbonyl-4-phenyl-4-[3,5-bis(trifluoromethyl) benzylthiomethyl]piperidine

a) Thioacetic acid (5.13ml) was added to a suspension of caesium carbonate (11.7g) in dimethylformamide (120ml) at room temperature. The solution was stirred for 10 min and a solution of 3,5-bis(trifluoromethyl)benzyl bromide (20g) in dimethylformamide (10ml) was added. The resulting solution was stirred for 16h, in the dark. The solvent was removed *in vacuo* and the residue was partitioned between ethyl acetate and water. The organic layer was washed with water, dried (Na_2SO_4) and the solvent was removed leaving an orange oil. The oil was chromatographed on silica gel in 5% ethyl acetate/petrol giving 3,5-bis(trifluoromethyl)benzyl thioacetate (14.8g) as a yellow oil. ^1H NMR (360MHz, $CDCl_3$) δ 2.39 (3H, s), 4.17 (2H, s), 7.75 (3H, s); m/z (CI^+) 303 (M^+ +1).

b) Sodium methoxide (3g) was added in small portions to a solution of 3,5-bis(trifluoromethyl)benzyl thioacetate (10g) in methanol (50ml), under an inert atmosphere. The resulting solution was stirred at room temperature for 16h. The solvent was removed and the residue was partitioned between ethyl acetate and 0.1N HCl solution. The organic layer was dried (Na_2SO_4) and the solvent was removed leaving a clear oil which was chromatographed on silica in 2% ethyl acetate/petrol. 3,5-Bis(trifluoromethyl)benzyl mercaptan (5.02g) was obtained as an off white solid (STENCH).

c) 4-Phenyl-4-carboxyl piperidine tosylate (20g) was suspended in tetrahydrofuran (50ml). Lithium aluminium

hydride (1M solution in tetrahydrofuran, 106ml) was added dropwise to the suspension at 0°C. When the addition was complete the solution was stirred at reflux temperature for 2h. The temperature was lowered to room temperature and 2N sodium hydroxide solution (6.4ml) was added with extreme care, followed by water (8ml) and a further 25ml of 2N sodium hydroxide solution. Di-t-butyl-dicarbonate (11.56g) in dichloromethane (65ml) was added and the resulting slurry was stirred for 16h at room temperature. The slurry was filtered through Na_2SO_4 and washed with dichloromethane (2.5L). The solvent was removed giving a clear viscous oil which was recrystallised from ether-petrol giving 1-t-butoxycarbonyl-4-phenyl-4-hydroxymethyl piperidine (12.4g) as a white solid. mp 64°C MS CI^+ 287 $(M+1)^+$.

d) Triethylamine (5.25ml) was added to a solution of 1-t-butoxycarbonyl-4-phenyl-4-hydroxymethyl piperidine (10g) in dichloromethane (200ml). The temperature was lowered to 0°C and methane sulphonyl chloride (2.92ml) was added. The solution was stirred for 30 min, washed with water, dried (Na_2SO_4), and the solvent was removed giving a clear oil. The oil was recrystallised from ethyl acetate/petrol giving N-t-butoxycarbonyl-4-phenylpiperidin-4-yl)methyl methanesulphonate (11.65g) as a white solid. m/z (CI^+) 387 ($M^+ + NH_4^+$).

e) A solution of 3,5-bis(trifluoromethyl)benzyl mercaptan, (2g) in N-methyl pyrollidinone (10ml) was added dropwise to a stirred suspension of sodium hydride (80% dispersion, 325mg) in N-methyl pyrollidinone (30ml) at room temperature. The solution was stirred for 1h. N-t-butoxycarbonyl-4-phenylpiperidin-4-yl)methyl methanesulphonate (2.5g) was added and the solution was stirred for 16h at 60°C. The solution was allowed to cool to

room temperature, poured into water, extracted twice with ethyl acetate. The organic layer was washed with water, dried (Na_2SO_4), and the solvent was removed *in vacuo* giving a brown oil which was chromatographed on silica gel in 15% ethyl acetate/petrol. 1-t-Butoxycarbonyl-4-phenyl-4-[3,5-bis(trifluoromethyl)benzylthiomethyl]piperidine (2.84g) was obtained as a clear oil. m/z (CI^+) 534 (M^+ +1).

EXAMPLE 4

1-t-Butoxycarbonyl-4-phenyl-4-[3,5-bis(trifluoromethyl) benzylsulphinylmethyl]piperidine

m-Chloroperoxybenzoic acid (80-90%, 0.4g) was added to a solution of Example 3 (1g) in dichloromethane (20ml) containing potassium carbonate (0.5g), at 0°C. The solution was stirred for 30 min, diluted with dichloromethane (20ml), washed with water, dried (Na_2SO_4) and removal of the solvent *in vacuo* gave an off white solid. The solid was recrystallised from diethyl ether/petrol giving 1-t-butoxycarbonyl-4-phenyl-4-[3,5-bis(trifluoromethyl)benzylsulphinylmethyl]piperidine as a white solid, m.p. 123-134°C, m/z (CI^+) 567 ($M^+ + NH_4^+$). Found: C, 57.00; H, 5.18; N, 2.36. $C_{26}H_{29}NO_3SF_6$ requires C, 56.82; H, 5.32; N, 2.55.

EXAMPLE 5

1-t-Butoxycarbonyl-4-phenyl-4-[3,5-bis(trifluoromethyl) benzylsulphonylmethyl]piperidine

m-Chloroperoxybenzoic acid (80-90%, 0.4g) was added to a solution of Example 3 (0.45g) in dichloromethane (15ml) containing

sodium bicarbonate (0.5g), at 0°C. The solution was stirred for 5h at room temperature, diluted with dichloromethane (15ml), washed with water, dried (Na_2SO_4) and the solvent was removed. 1-t-Butoxycarbonyl-4-phenyl-4-[3,5-bis(trifluoromethyl) benzylsulphonylmethyl]piperidine was obtained as a yellow foam. m/z (CI^+) 534 $(M+1)^+$.

EXAMPLE 6

4-Phenyl-4-[3,5-bis(trifluoromethyl)benzylsulphonyl methyl]piperidine hydrochloride

1-t-Butoxycarbonyl-4-phenyl-4-[3,5-bis(trifluoromethyl) benzylsulphonyl methyl]piperidine was dissolved in diethyl ether (5ml) and ethereal HCl (5ml) was added. The solution was left standing for 16h, solvent was removed and residue was recrystallised from isopropyl alcohol/isopropyl ether giving 4-phenyl-4-[3,5-bis(trifluoromethyl)benzylsulphonylmethyl] piperidine hydrochloride (196mg) as a white solid, m.p. 249°C (dec), m/z (CI^+) 466 (M^+ +1). Found: C, 49.90; H, 4.36; N, 2.89. $C_{21}H_{21}NO_2SF_6$. HCl requires C, 50.25; H, 4.42; N, 2.79.

EXAMPLE 7

4-Phenyl-4-[(3,5-bistrifluoromethyl)benzylaminomethyl] piperidine dihydrochloride

A solution of 3,5-bistrifluoromethylbenzyl bromide (1.86ml) in dry CH_2Cl_2 was added dropwise to a chilled solution of 4-phenyl-4-aminomethyl-1-^{t}-butoxycarbonyl piperidine (2.46g) in dry CH_2Cl_2. The reaction was allowed to warm to room temperature and stirred for two hours, diluted with water

(50ml), the organic layer separated and dried over ($MgSO_4$). Filtration and removal of solvent afforded a yellow oil, which was further purified by MPLC (SiO_2/EtOAc/nHex). The recovered product was treated with HCl/Et_2O for 18 hrs. The solvent was removed under reduced pressure and the product re-crystallised from EtOAc. mp 210-215°C; $C_{21}H_{22}N_2F_6.2HCl.½H_2O$ requires C, 50.61; H, 5.06; N, 5.62; Found C, 50.24; H, 5.14; N, 5.70%.

EXAMPLE 8

4-Phenyl-4-[(3,5-dichloro)benzylaminomethyl] piperidine hydrochloride

The title compound was prepared by the method of Example 4. mp 220-223°C; $C_{19}H_{22}N_2Cl_2.1.5HCl$ requires C, 56.48; H, 5.86; N, 6.93; Found C, 56.28; H, 5.50; N, 6.60%.

EXAMPLE 9

4-Phenyl-4-[(3,5-dichloro)benzylamino-1-ethyl] piperidine dihydrochloride.

The title compound was prepared by the method of Example 4. mp 200-208°C; $C_{20}H_{24}N_2Cl_2.2HCl$ requires C, 55.60; H, 6.01; N, 6.42; Found C, 54.91; H, 6.10; N, 6.30%.

EXAMPLE 10

4-Phenyl-4-[(3-isopropoxy)benzamidomethyl) piperidine hydrochloride

The title compound was prepared by the method of Example 2. mp 124-125°C. m/z (CI^+) 353 $(M+H)^+$.

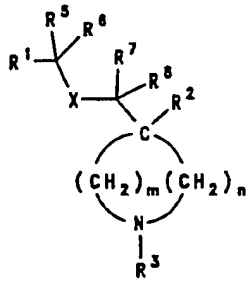
EXAMPLE 11

4-Phenyl-4-[(3-isopropoxy) N-methyl-benzamidomethyl) piperidine hydrochloride

Methyl iodide (1.0g) was added to a stirred solution of NaH (44mg x 60%) and the compound of Example 7 (240mg) in dry DMF. The resulting solution was stirred for 18 hrs at room temperature. The reaction was then diluted with water and extracted into EtOAc. The organic layers were separated and dried over ($MgSO_4$). Filtration and removal of solvent afforded a clear oil. Purification by MPLC (SiO_2/EtOAc/nHex) followed by treatment with Et_2O/HCl and recrystallisation from EtOAc afforded the title compound. mp 210-211°C; $C_{23}H_{30}N_2O_2.HCl\text{-}2H_2O$ requires C, 62.93; H, 8.03; N, 6.38; Found C, 63.37; H, 8.09; N, 6.63%.

Claims

1. A compound of formula (I), or a salt or prodrug thereof:



(I)

wherein x is NR^4 or SO or SO_2

m is 2, 3 or 4;

n is 0, 1 or 2 when m is 2 or 3, and n is 0 or 1 when m is 4;

R^1 represents phenyl optionally substituted by 1, 2 or 3 groups selected from C_{1-6}alkyl, C_{2-6} alkenyl, C_{2-6}alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, $-OR^a$, SR^a, SOR^a, SO_2R^a, $-NR^aR^b$, $-NR^aCOR^b$, $-NR^aCO_2R^b$, $-CO_2R^a$ or $-CONR^aR^b$, where R^a and R^b each independently represent H, C_{1-6}alkyl, phenyl or trifluoromethyl;

R^2 represents phenyl optionally substituted by 1, 2 or 3 groups selected from C_{1-6}alkyl, C_{2-6} alkenyl, C_{2-6}alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, $-OR^a$, SR^a, SOR^a, SO_2R^a, $-NR^aR^b$, $-NR^aCOR^b$, $-NR^aCO_2R^b$, $-CO_2R^a$ or $-CONR^aR^b$, where R^a and R^b each independently represent H, C_{1-6}alkyl, phenyl or trifluoromethyl; heteroaryl selected from indazolyl, thienyl, furyl, pyridyl, thiazolyl, tetrazolyl and quinolyl; benzhydryl; or benzyl; wherein each heteroaryl

and each phenyl moiety of benzyl and benzhydryl may be substituted by C_{1-6}alkyl, C_{1-6}alkoxy, halo or trifluoromethyl;

R^3 represents H, COR^9, CO_2R^{10}, $COCONR^{10}R^{11}$, $COCO_2R^{10}$, SO_2R^{15}, $CONR^{10}SO_2R^{15}$, C_{1-6}alkyl optionally substituted by a group selected from (CO_2R^{10}, $CONR^{10}R^{11}$, hydroxy, cyano, COR^9, $NR^{10}R^{11}$, $C(NOH)NR^{10}R^{11}$, CONHphenyl(C_{1-4}alkyl), $COCO_2R^{10}$, $COCONR^{10}R^{11}$, SO_2R^{15}, $CONR^{10}SO_2R^{15}$ and phenyl optionally substituted by one or more substituents selected from C_{1-6}alkyl, C_{1-6}alkoxy, halo and trifluoromethyl), Y-R^{16} or CO-Z-$(CH_2)_q$-R^{12};

R^4 represents H, C_{1-6}alkyl or COR^9.

R^5, R^6, R^7 and R^8 each independently represent H or C_{1-6}alkyl; or when X is NR^4, either R^5 and R^6 may together represent an oxygen atom or R^7 and R^3 may together represent an oxygen atom;

R^9 represents H, C_{1-6}alkyl or phenyl;

R^{10} and R^{11} each independently represent H or C_{1-6}alkyl;

R^{12} represents $NR^{13}R^{14}$ or an optionally substituted aromatic or non-aromatic azacyclic or azabicyclic group;

R^{13} and R^{14} each independently represent H, C_{1-6}alkyl, phenyl optionally substituted by one or more of C_{1-6}alkyl, C_{1-6}alkoxy, halo or trifluoromethyl or phenylC_{1-4}alkyl optionally substituted in the phenyl ring by one or more of C_{1-6}alkyl, C_{1-6}alkoxy, halo or trifluoromethyl;

R^{15} represents C_{1-6}alkyl, trifluoromethyl or phenyl optionally substituted by one or more substituents selected from C_{1-6}alkyl, C_{1-6}alkoxy, halo and trifluoromethyl;

R^{16} represents an optionally substituted aromatic heterocycle;

Y represents a hydrocarbon chain of 1,2,3 or 4 carbon atoms which may optionally be substituted by oxo;

2. A compound as claimed in claim 1 wherein X is SO or SO_2.

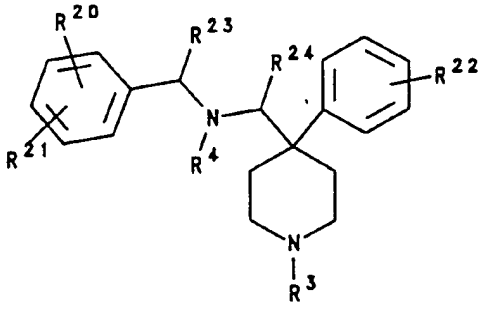
3. A compound as claimed in claim 1 wherein X is NR^4 and R^5, R^6, R^7 and R^8 each represent H or C_{1-6} alkyl.

4. A compound as claimed in claim 8 wherein R^5, R^6, R^7 and R^8 each represent H or R^5 represents methyl and R^6, R^7 and R^8 each represent H.

5. A compound as claimed in claim 1 wherein X is NR^4 and R^5 and R^6 together represent an oxygen atom or R^7 and R^8 together represent an oxygen atom.

6. A compound as claimed in any of claims 1 to 5 wherein M is 2 and N is 2.

7. A compound as claimed in claims of the formula (Ia) or a pharmaceutically acceptable salt thereof:



(Ia)

wherein

R^3 and R^4 are as defined for formula (I);

R^{20} and R^{21} independently represent H C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, OR^a, SR^a SOR^a, SO_2R^a,

NR^aR^b, NR^aCOR^b, $NR^aCO_2R^b$, COR^a or $CONR^aR^b$, where R^a and R^b are as previously defined;

R^{22} represents H or halo, preferably H or fluoro; and

R^{23} and R^{24} each independently represent H or methyl.

8. A compound as claimed in any of claims 1 to 7 wherein R^3 is H or YR^{16}.

9. A compound as claimed in claim 8 wherein R^3 is YR^{16} wherein Y is an alkyl group of 1 to 4 carbon atoms and R^{16} represents an unsubstituted 5-membered nitrogen containing heterocycle or a 5-membered nitrogen containing heterocycle substituted by oxo.

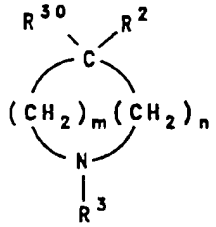
10. A compound as claimed in claim 1 which is
4-Phenyl-4-(2-Methoxybenzylaminomethyl)piperidine;
4-Phenyl-4-[(3,5-bistrifluoromethylbenzyl)amido] methylpiperidine;
1-t-Butoxycarbonyl-4-phenyl-4-[3,5-bis(trifluoromethyl)benzylthiomethyl]piperidine;
1-t-Butoxycarbonyl-4-phenyl-4-[3,5-bis(trifluoromethyl) benzylsulphinylmethyl]piperidine;
1-t-Butoxycarbonyl-4-phenyl-4-[3,5-bis(trifluoromethyl)benzylsulphonylmethyl]piperidine;
4-Phenyl-4-[3,5-bis(trifluoromethyl)benzylsulphonylmethyl]piperidine;
4-Phenyl-4-[(3,5-bistrifluoromethyl)benzylaminomethyl] piperidine;
4-Phenyl-4-[(3,5-dichloro)benzylaminomethyl] piperidine;
4-Phenyl-4-[(3,5-dichloro)benzylamino-1-ethyl] piperidine;
4-Phenyl-4-[(3-isopropoxy)benzamidomethyl piperidine;
4-Phenyl-4-[(3-isoproxy) N-methyl-benzamidomethyl) piperidine;
or a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition comprising a compound as claimed in any of claims 1 to 10 and a pharmaceutically acceptable carrier therefor.

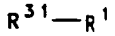
12. The use of a compound as claimed in any of claims 1 to 4 in the preparation of a medicament for the treatment of a physiological disorder associated with an excess of tachykinins.

13. A method of treatment or prevention of a physiological disorder associated with an excess of tachykinins which comprises administration to a patient in need thereof a tachykinin reducing amount of a compound as claimed in any of claims to 10 or a composition as claimed in claim 11.

14. A process for the preparation of a compound of the formula (I) as defined in claim 1 wherein X is NR^4 and R^5 and R^6 are both H as R^7 and R^8 are both H which comprises reacting a compound of formula (II) with a compound of formula (III):



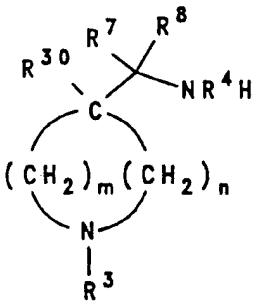
(II)



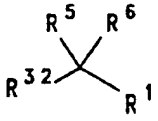
(III)

wherein R^1, R^2, m and n are as defined for formula (I), R^3 is as defined for formula (I) except that, when R^3 is H it is replaced by a suitable protecting group, such as $CO_2(C_{1-6}alkyl)$, R^{30} is CHO and R^{31} is $CR^5R^6NHR^4$, where R^4, R^5 and R^6 are as defined for formula (I), or R^{30} is $CR^7R^8NHR^4$, where R^4, R^7 and R^8 are as defined for formula (I), and R^{31} is CHO, followed by deprotection, if required.

15. A process for the preparation of a compound of formula (I) as defined in claim 1 wherein X is NR^4 may be prepared by reaction of compounds of formula (IV) with compounds of formula (V):



(IV)

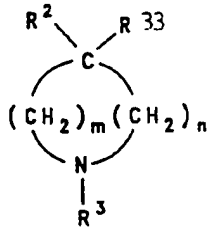


(V)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, m and n are as previously defined except that neither R^5 and R^6 and R^7 and R^8 represent an oxygen atom, and R^{32} represents a leaving group such as halo, for example chloro, bromo or iodo, or a sulphonate, for example methylsulphonate or p-toluenesulphonate, in the presence of a base.

16. A process for the preparation of a compound of the formula (I) as defined in claim 1 wherein R^3 is not H which comprises reacting a compound of the formula (I) wherein R^3 is not H which comprises reacting a compound of the formula (I) wherein R^3 is H with a compound of the formula R^3-Hal where Hal is a leaving group such as halo.

17. A process for the preparation of a compound of the formula (I) as defined in claim 1 wherein X is NR^3 and either R^5 and R^6 represent an oxygen atom or R^7 and R^8 represent an oxygen atom may be prepared by a process which comprises reacting a compound of formula (IIa) with a compound of formula (IIIa):



(IIa)

(IIb)

wherein R^1, R^2, m and n are as defined for formula (I), R^3 is as defined for formula (I) **except that**, when R^3 is H it is replaced by a suitable protecting group, such as $CO_2(C_{1-6}alkyl)$, and R^{33} and R^{34} are chosen as follows:

R^{33} represents (C=O)OH and R^{34} represents $HNR^4CR^6R^7$; or

R^{33} represents $CR^6R^7NR^4H$ and R^{34} represents C(=O)Hal; or

R^{33} represents NR^4H and R^{34} represents -N=C=O; or

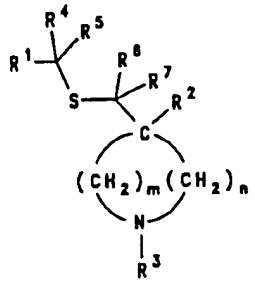
R^{33} represents -N=C=O and R^{34} represents NR^4H; or

R^{33} represents O(C=O)Hal and R^{34} represents NH_2; or

R^{33} represents NH_2 and R^{34} represents O(C=O)Hal;

wherein R^4, R^6 and R^7 are as defined for formula (I) and Hal represents halo such as iodo, bromo or, preferably, chloro; followed by deprotection if, if required.

18. A process for the preparation of a compound of the formula (I) as defined in claim 1 wherein X is SO or SO_2 which comprises oxydation of a compound of the formula (IIb):



(II)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, m and n are as defined for formula (I).

INTERNATIONAL SEARCH REPORT

Inter · ional Application No
PCT/GB 93/02535

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07D211/26 C07D211/20 C07D211/24 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 512 902 (ELF SANOFI) 11 November 1992 see the whole document ---	1-18
A	WO,A,92 01672 (NOVO-NORDISK) 6 February 1992 see abstract ---	1-13
A	WO,A,92 12128 (DU PONT MERCK) 23 July 1992 see the whole document --- -/--	1-13

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 April 1994	-9. 05. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Kissler, B

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ARCHIV. PHARM. vol. 319, no. 6 , 1986 pages 505 - 515 Rehse, Klaus; Werner, Ulrich 'Platelet aggregation inhibiting and anticoagulant effects of oligoamines. I. N-(4-Piperidinyl)methanamines' * RN 106507-04-4 ; Benzamide, N-[[1-(1,4-benzodioxan-2-ylmethyl)-4-phenyl-4-piperidyl]methyl]-, hydrochloride * * RN 105378-85-6; 4-Piperidinemethanamine, 1-[2-(4-chlorophenyl)ethyl]-N-(9H-fluoren-2- ylmethyl)-4-phenyl- * * RN 105378-83-4; 4-Piperidinemethanamine, 1-[2-(4-chlorophenyl)ethyl]-N-[(4-chlorophenyl)methyl]-4-phenyl- * * RN 104999-22-6; Benzamide, N-[[1-(1,4-benzodioxan-2-ylmethyl)-4-phenyl-4-piperidyl]methyl]-3,4,5-trimethoxy-, hydrochloride * ---	1,3-13
X	CHEMICAL ABSTRACTS, vol. 60, no. 9, 27 April 1964, Columbus, Ohio, US; abstract no. 11242h, see abstract * RN 94682-36-7; Piperidine, 4-[(benzylamino)methyl]-1-methyl-4-phenyl- * & PROC. INTERN. PHARMACOL. MEETING vol. 8 , 1961 , STOCKHOLM pages 189 - 198 V. G. LONGO, S. CHIAVARELLI --- -/--	1,3,4, 6-13

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 94, no. 23, 8 June 1981, Columbus, Ohio, US; abstract no. 192068p, * RN 77629-00-6; Phenol, 4-[[[(1-butyl-4-phenyl-4-piperidinyl)methyl]amino]methyl]-, dihydrochloride * * RN 77621-37-5; 4-Piperidinemethanamine, 1-butyl-4-phenyl-N-[(3,4,5-trimethoxyphenyl)methyl]-, dihydrochloride * * RN 77621-35-3; 4-Piperidinemethanamine, N-[(4-aminophenyl)methyl]-1-butyl-4-phenyl - * * RN 77621-34-2; 4-Piperidinemethanamine, 1-butyl-N-[(4-chlorophenyl)methyl]-4-phenyl- * * RN 77621-33-1; Phenol, 2-[[[(1-butyl-4-phenyl-4-piperidinyl)methyl]amino]methyl]- * & ACTA POL. PHARM. vol. 37, no. 2 , 1980 pages 177 - 180 Gutkowska, Bozenna; Nowak, Tomasz 'Synthesis of certain 1-butyl-4-phenyl-4-arylmethylaminomethylpiperidines' ---	1,3-13
X	CHEMICAL ABSTRACTS, vol. 89, no. 5, 31 July 1978, Columbus, Ohio, US; abstract no. 43033t, * RN 65713-60-2; Benzamide, N-[(1-butyl-4-phenyl-4-piperidinyl)methyl]-3,4,5-trimethoxy- * * RN 65713-59-9; Benzamide, 4-amino-N-[(1-butyl-4-phenyl-4-piperidinyl)methyl]- * * RN 65713-58-8; Benzamide, N-[(1-butyl-4-phenyl-4-piperidinyl)methyl]-2-hydroxy- * * RN 65713-57-7; Benzamide, N-[(1-butyl-4-phenyl-4-piperidinyl)methyl]-4-hydroxy-, monohydrochloride * & ROCZ. CHEM. vol. 51, no. 10 , 1985 pages 1985 - 1989 Gutkowska, Bozenna; Nowak, Tomasz 'Syntheses of 1-butyl-4-phenyl-4-piperidylmethylamides of some aromatic acids' --- -/--	1,3-13

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 86, no. 13, 28 March 1977, Columbus, Ohio, US; abstract no. 89539d, * RN 61942-46-9; Benzamide, N-[(1-butyl-4-phenyl-4-piperidinyl)methyl]-4-chloro- * * RN 61942-45-8; Benzamide, N-[(1-butyl-4-phenyl-4-piperidinyl)methyl]-4-nitro-, monohydrochloride * & ROCZ. CHEM. vol. 50, no. 6 , 1976 pages 1191 - 1193 Gutkowska, Bozenna; Nowak, Tomasz 'Syntheses of 1-butyl-4-phenyl-4-piperidylmethylamides of some aromatic acids'	1,3-13
A	EP,A,0 512 901 (ELF SANOFI) 11 November 1992 see the whole document	1-18
X	GB,A,1 356 118 (SEARLE) 12 June 1974 * RN 37983-43-0; 4-Piperidinecarbothioic acid, 1-(3-cyano-3,3-diphenylpropyl)-4-phenyl- , S-(phenylmethyl) ester, monohydrochloride *	1,2,6, 11-13
X	FR,A,1 501 151 (STECKER INTERNATIONAL) 10 November 1967 * RN 22896-95-3; Salicylamide, N-[(1-benzyl-4-phenyl-4-piperidyl)methyl]-3,5-dibromo - *	1,3-13
A	JOURNAL OF MEDICINAL CHEMISTRY. vol. 10, no. 2 , 1967 , WASHINGTON US pages 174 - 177 DeGraw, Joseph I.; Brown, Vernon H.; Kontaxis, Nicholas E.; Ferguson, Samuel A.; Gordon, Gale Ross; Peters, John Henry; Skinner, W 'Histamine releasers. III. Dibasic acid amides of 4-phenyl-4-aminomethylpiperidines' * RN 15235-02-6; Isophthalamide, N,N'-bis[(1-benzyl-4-phenyl-4-piperidyl)methyl]-, dihydrochloride *	1-13

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1

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BE,A,640 941 (HOECHST) 8 June 1964 * RN 2086-43-3; o-Toluamide, 6-chloro-N-[[4-(m-methoxyphenyl)-1-methyl-4-piperidyl]methyl]-, hydrochloride * * RN 1241-75-4; Benzamide, N-[[4-(m-methoxyphenyl)-1-methyl-4-piperidyl]methyl]-, hydrochloride * * RN 1103-96-4; Benzamide, p-ethoxy-N-[[4-(m-methoxyphenyl)-1-methyl-4-piperidyl]methyl]-, hydrochloride *	1,3-13
X	CHEMICAL ABSTRACTS, vol. 62, no. 8, 12 April 1965, Columbus, Ohio, US; abstract no. 9114c, * RN 1103-95-3; Benzamide, p-ethoxy-N-[[4-(m-methoxyphenyl)-1-methyl-4-piperidyl]methyl]- * * RN 1103-96-4; Benzamide, p-ethoxy-N-[[4-(m-methoxyphenyl)-1-methyl-4-piperidyl]methyl]-, hydrochloride * * RN 1099-56-5; Benzamide, N-[[4-(m-methoxyphenyl)-1-methyl-4-piperidyl]methyl]- * * RN 1097-79-6; Benzamide, N-[[4-(m-hydroxyphenyl)-1-methyl-4-piperidyl]methyl]-, hydrochloride * * RN 1097-78-5; Benzamide, N-[[4-(m-hydroxyphenyl)-1-methyl-4-piperidyl]methyl]- * & FR,A,1 381 445 (HOECHST) 11 December 1964	1,3-13

INTERNATIONAL SEARCH REPORT

:ernational application No.
PCT/GB93/02535

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 13 is directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

./.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/

Lack of conciseness/obscurity

The notation
"or R7 and R3 may together represent an oxygen atom",
giving rise to oxaza-bicyclo[x.y.z]alkanes remains obscure within the scope and the context of the present application and has not been searched.

Claims searched incompletely: 1 - 6, 11 - 18

INTERNATIONAL SEARCH REPORT

information on patent family members

Int · ional Application No
PCT/GB 93/02535

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INTERNATIONAL SEARCH REPORT

information on patent family members

Inv · ional Application No
PCT/GB 93/02535

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		US-A- 3455940	15-07-69
BE-A-640941		NONE	
FR-A-1381445		NONE	